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* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page for STN Seminar Schedule - N. America
NEWS 2	JAN 02	STN pricing information for 2008 now available
NEWS 3	JAN 16	CAS patent coverage enhanced to include exemplified prophetic substances
NEWS 4	JAN 28	USPATFULL, USPAT2, and USPATOLD enhanced with new custom IPC display formats
NEWS 5	JAN 28	MARPAT searching enhanced
NEWS 6	JAN 28	USGENE now provides USPTO sequence data within 3 days of publication
NEWS 7	JAN 28	TOXCENTER enhanced with reloaded MEDLINE segment
NEWS 8	JAN 28	MEDLINE and LMEDLINE reloaded with enhancements
NEWS 9	FEB 08	STN Express, Version 8.3, now available
NEWS 10	FEB 20	PCI now available as a replacement to DPCI
NEWS 11	FEB 25	IFIREF reloaded with enhancements
NEWS 12	FEB 25	IMSPRODUCT reloaded with enhancements
NEWS 13	FEB 29	WPINDEX/WPIDS/WPIX enhanced with ECLA and current U.S. National Patent Classification
NEWS 14	MAR 31	IFICDB, IFIPAT, and IFIUDB enhanced with new custom IPC display formats
NEWS 15	MAR 31	CAS REGISTRY enhanced with additional experimental spectra
NEWS 16	MAR 31	CA/CAplus and CASREACT patent number format for U.S. applications updated
NEWS 17	MAR 31	LPCI now available as a replacement to LDPCI
NEWS 18	MAR 31	EMBASE, EMBAL, and LEMBASE reloaded with enhancements
NEWS 19	APR 04	STN AnaVist, Version 1, to be discontinued
NEWS 20	APR 15	WPIDS, WPINDEX, and WPIX enhanced with new predefined hit display formats
NEWS 21	APR 28	EMBASE Controlled Term thesaurus enhanced
NEWS 22	APR 28	IMSRESEARCH reloaded with enhancements

NEWS EXPRESS FEBRUARY 08 CURRENT WINDOWS VERSION IS V8.3,
AND CURRENT DISCOVER FILE IS DATED 20 FEBRUARY 2008

NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS LOGIN	Welcome Banner and News Items
NEWS IPC8	For general information regarding STN implementation of IPC 8

Enter NEWS followed by the item number or name to see news on that specific topic.

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* * * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 15:24:13 ON 01 MAY 2008

=> file reg
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

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STRUCTURE FILE UPDATES: 30 APR 2008 HIGHEST RN 1018615-45-6
DICTIONARY FILE UPDATES: 30 APR 2008 HIGHEST RN 1018615-45-6

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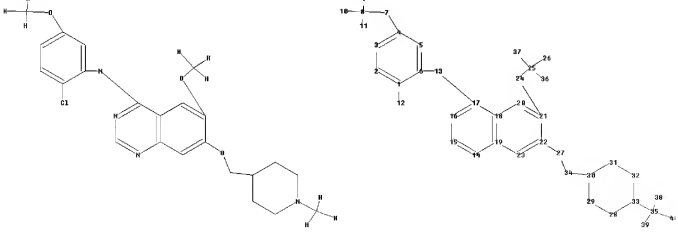
http://www.cas.org/support/stngen/stndoc/properties.html

=>
Uploading C:\Program Files\STNEXP\Queries\10534721 a-1.str



chain nodes :
7 8 9 10 11 12 13 24 25 26 27 34 35 36 37 38 39 40
ring nodes :

```
1  2  3  4  5  6  14  15  16  17  18  19  20  21  22  23  28  29  30  31  32  33
chain bonds :
1-12  4-7  6-13  7-8  8-11  8-9  8-10  13-17  21-24  22-27  24-25  25-26  25-36
25-37  27-34  30-34  33-35  35-38  35-39  35-40
ring bonds :
1-2  1-6  2-3  3-4  4-5  5-6  14-15  14-19  15-16  16-17  17-18  18-19  18-20  19-
23  20-21  21-22  22-23  28-29  28-33  29-30  30-31  31-32  32-33
exact/norm bonds :
4-7  6-13  7-8  13-17  21-24  22-27  24-25  27-34  28-29  28-33  29-30  30-31  31-
32  32-33  33-35
exact bonds :
1-12  8-11  8-9  8-10  25-26  25-36  25-37  30-34  35-38  35-39  35-40
normalized bonds :
1-2  1-6  2-3  3-4  4-5  5-6  14-15  14-19  15-16  16-17  17-18  18-19  18-20  19-
23  20-21  21-22  22-23


Match level :
1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:CLASS  8:CLASS  9:CLASS  10:CLASS
11:CLASS  12:CLASS  13:CLASS  14:Atom  15:Atom  16:Atom  17:Atom  18:Atom  19:Atom
20:Atom  21:Atom  22:Atom  23:Atom  24:CLASS  25:CLASS  26:CLASS  27:CLASS  28:Atom
29:Atom  30:Atom  31:Atom  32:Atom  33:Atom  34:CLASS  35:CLASS  36:CLASS  37:CLASS
38:CLASS  39:CLASS  40:CLASS



L1      STRUCTURE UPLOADED

=> s l1
SAMPLE SEARCH INITIATED 15:25:03 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -       17 TO ITERATE

100.0% PROCESSED       17 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:           93 TO      587
PROJECTED ANSWERS:               0 TO        0

L2            0 SEA SSS SAM L1

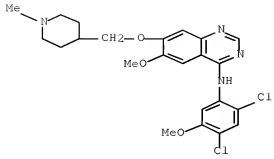
=> s l1 full
FULL SEARCH INITIATED 15:25:29 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -      521 TO ITERATE

100.0% PROCESSED      521 ITERATIONS                                3 ANSWERS
SEARCH TIME: 00.00.01

L3            3 SEA SSS FUL L1

=> d scan

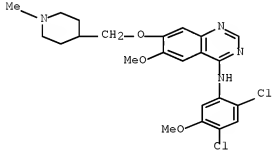
L3   3 ANSWERS   REGISTRY  COPYRIGHT 2008 ACS on STN
IN   4-Quinazolinamine, N-(2,4-dichloro-5-methoxyphenyl)-6-methoxy-7-[(1-methyl-
     4-piperidinyl)methoxy]-, dihydrochloride (9CI)
MF   C23 H26 Cl2 N4 O3 . 2 Cl H
```



●2 HCl

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

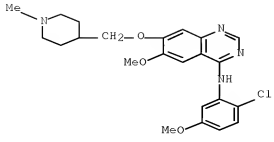
L3 3 ANSWERS REGISTRY COPYRIGHT 2008 ACS on STN
IN 4-Quinazolinamine, N-(2,4-dichloro-5-methoxyphenyl)-6-methoxy-7-[(1-methyl-4-piperidinyl)methoxy]-
MF C23 H26 Cl2 N4 O3
CI COM



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):41

L3 3 ANSWERS REGISTRY COPYRIGHT 2008 ACS on STN
IN 4-Quinazolinamine, N-(2-chloro-5-methoxyphenyl)-6-methoxy-7-[(1-methyl-4-piperidinyl)methoxy]-
MF C23 H27 Cl N4 O3



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

ALL ANSWERS HAVE BEEN SCANNED

=> file cap
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	179.74	179.95

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FILE LAST UPDATED: 30 Apr 2008 (20080430/ED)

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=> d his

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FILE 'REGISTRY' ENTERED AT 15:24:29 ON 01 MAY 2008
L1 STRUCTURE UPLOADED
L2 0 S L1
L3 3 S L1 FULL

FILE 'CAPLUS' ENTERED AT 15:26:39 ON 01 MAY 2008

```
=> s l3
L4          11 L3

=> s us 2005-534721/apps
             1 US2005-534721/AP
             0 US2005-534721/PRN
L5           1 US 2005-534721/APS
               (US2005-534721/AP,PRN)

=> file reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     5.68     185.63

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STRUCTURE FILE UPDATES:   30 APR 2008  HIGHEST RN 1018615-45-6
DICTIONARY FILE UPDATES:  30 APR 2008  HIGHEST RN 1018615-45-6

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http://www.cas.org/support/stngen/stndoc/properties.html

=> tra rn l5
L6          TRANSFER L5 1- RN :     152 TERMS
L7         152 L6

=> s quinazoline/cn
L8           1 QUINAZOLINE/CN

=> d rsd l8

L8   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2008 ACS on STN

Ring System Data

Elemental|Elemental| Size of |Ring System|   Ring    |   RID
Analysis |Sequence |the Rings|  Formula  |Identifier|Occurrence
   EA    |   ES    |   SZ    |    RF     |   RID    |  Count
=========+=========+=========+===========+==========+==========
C4N2-C6  |NCNC3-C6 |6-6      |C8N2       |591.100.47|1
```

```
=> s 591.100.47/rid
L9      131696 591.100.47/RID

=> d his

     (FILE 'HOME' ENTERED AT 15:24:13 ON 01 MAY 2008)

     FILE 'REGISTRY' ENTERED AT 15:24:29 ON 01 MAY 2008
L1               STRUCTURE UPLOADED
L2             0 S L1
L3             3 S L1 FULL

     FILE 'CAPLUS' ENTERED AT 15:26:39 ON 01 MAY 2008
L4            11 S L3
L5             1 S US 2005-534721/APPS

     FILE 'REGISTRY' ENTERED AT 15:28:15 ON 01 MAY 2008

     FILE 'CAPLUS' ENTERED AT 15:28:49 ON 01 MAY 2008
L6               TRA L5 1- RN :      152 TERMS

     FILE 'REGISTRY' ENTERED AT 15:28:50 ON 01 MAY 2008
L7           152 SEA L6
L8             1 S QUINAZOLINE/CN
L9       131696 S 591.100.47/RID

=> s l7 and l9
L10          97 L7 AND L9

=> file caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    12.12     210.34

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=> d his
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```
     (FILE 'HOME' ENTERED AT 15:24:13 ON 01 MAY 2008)

     FILE 'REGISTRY' ENTERED AT 15:24:29 ON 01 MAY 2008
L1             STRUCTURE UPLOADED
L2           0 S L1
L3           3 S L1 FULL

     FILE 'CAPLUS' ENTERED AT 15:26:39 ON 01 MAY 2008
L4          11 S L3
L5           1 S US 2005-534721/APPS

     FILE 'REGISTRY' ENTERED AT 15:28:15 ON 01 MAY 2008

     FILE 'CAPLUS' ENTERED AT 15:28:49 ON 01 MAY 2008
L6             TRA L5 1- RN :      152 TERMS

     FILE 'REGISTRY' ENTERED AT 15:28:50 ON 01 MAY 2008
L7          152 SEA L6
L8            1 S QUINAZOLINE/CN
L9       131696 S 591.100.47/RID
L10           97 S L7 AND L9

     FILE 'CAPLUS' ENTERED AT 15:30:40 ON 01 MAY 2008

=> d l4 ibib abs hit

L4   ANSWER 1 OF 11  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:         2006:1075642  CAPLUS  Full-text
DOCUMENT NUMBER:          145:369462
TITLE:                    The novel Src kinase inhibitor M475271 inhibits
                          VEGF-induced vascular endothelial-cadherin and
                          β-catenin phosphorylation but increases their
                          association
AUTHOR(S):                Ali, Nermin; Yoshizumi, Masanori; Yano, Seiji; Sone,
                          Saburo; Ohnishi, Hideki; Ishizawa, Keisuke; Kanematsu,
                          Yasuhisa; Tsuchiya, Koichiro; Tamaki, Toshiaki
CORPORATE SOURCE:         Department of Pharmacology, Institute of Health
                          Biosciences, The University of Tokushima Graduate
                          School, Tokushima, 770-8503, Japan
SOURCE:                   Journal of Pharmacological Sciences (Tokyo, Japan)
                          (2006), 102(1), 112-120
                          CODEN: JPSTGJ; ISSN: 1347-8613
PUBLISHER:                Japanese Pharmacological Society
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   M475271, 4-quinazolinamine, N-(2-chloro-5-methoxyphenyl)-6-methoxy-7-[(1-
     methyl-4-piperidinyl) methoxy]-(9Cl), is a new anilinoquinazoline derivative
     that displays selective inhibition of Src kinase activity and tumor growth in
     vivo. Vascular endothelial growth factor (VEGF)-induced angiogenesis plays a
     pivotal role in tumor growth and metastasis. Vascular endothelial (VE)-
     cadherin is an endothelial cell-specific adhesion mol. that can interact with
     the cytoskeleton via several anchoring mols. such as β-catenin. Here, we
     examined the effect of M475271 on VE-cadherin and β-catenin phosphorylation
     and association We also examined its effect on VEGF-induced human umbilical
     vein endothelial cell (HUVEC) proliferation, migration, and tube formation.
     The findings reveal pretreatment with M475271 significantly inhibits VEGF-
     induced VE-cadherin and β-catenin phosphorylation. However, M475271
     significantly increases VE-cadherin and β-catenin association compared to the
```

VEGF-treated group. Confocal laser microscopic examination confirmed the augmentation effect of M475271 on VE-cadherin and β-catenin association Finally, M475271 was shown to have inhibitory effects comparable to those of PP2 and Herbimycin A on VEGF-induced HUVEC proliferation, migration, and tube formation. These findings suggest that M475271 attenuates VEGF-induced angiogenesis by maintaining cell-cell junction stability. Although the involvement of other signaling mols. cannot be ruled out, M475271 has potential as a drug for the inhibition of the angiogenesis needed for tumor growth and metastasis.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT 476359-98-5, M475271
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel Src kinase inhibitor M475271 inhibits VEGF-induced vascular endothelial-cadherin and β-catenin phosphorylation but increases their association)

=> d l4 1-11 ibib abs hit

L4 ANSWER 1 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2006:107642 CAPLUS Full-text
DOCUMENT NUMBER: 145:369462
TITLE: The novel Src kinase inhibitor M475271 inhibits VEGF-induced vascular endothelial-cadherin and β-catenin phosphorylation but increases their association
AUTHOR(S): Ali, Nermin; Yoshizumi, Masanori; Yano, Seiji; Sone, Saburo; Ohnishi, Hideki; Ishizawa, Keisuke; Kanematsu, Yasuhisa; Tsuchiya, Koichiro; Tamaki, Toshiaki
CORPORATE SOURCE: Department of Pharmacology, Institute of Health Biosciences, The University of Tokushima Graduate School, Tokushima, 770-8503, Japan
SOURCE: Journal of Pharmacological Sciences (Tokyo, Japan) (2006), 102(1), 112-120
CODEN: JPSTGJ; ISSN: 1347-8613
PUBLISHER: Japanese Pharmacological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB M475271, 4-quinazolinamine, N-(2-chloro-5-methoxyphenyl)-6-methoxy-7-[(1-methyl-4-piperidinyl) methoxy]-(9Cl), is a new anilinoquinazoline derivative that displays selective inhibition of Src kinase activity and tumor growth in vivo. Vascular endothelial growth factor (VEGF)-induced angiogenesis plays a pivotal role in tumor growth and metastasis. Vascular endothelial (VE)-cadherin is an endothelial cell-specific adhesion mol. that can interact with the cytoskeleton via several anchoring mols. such as β-catenin. Here, we examined the effect of M475271 on VE-cadherin and β-catenin phosphorylation and association We also examined its effect on VEGF-induced human umbilical vein endothelial cell (HUVEC) proliferation, migration, and tube formation. The findings reveal pretreatment with M475271 significantly inhibits VEGF-induced VE-cadherin and β-catenin phosphorylation. However, M475271 significantly increases VE-cadherin and β-catenin association compared to the VEGF-treated group. Confocal laser microscopic examination confirmed the augmentation effect of M475271 on VE-cadherin and β-catenin association Finally, M475271 was shown to have inhibitory effects comparable to those of PP2 and Herbimycin A on VEGF-induced HUVEC proliferation, migration, and tube formation. These findings suggest that M475271 attenuates VEGF-induced angiogenesis by maintaining cell-cell junction stability. Although the

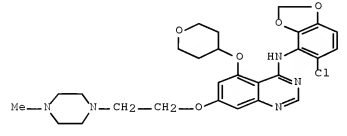
involvement of other signaling mols. cannot be ruled out, M475271 has potential as a drug for the inhibition of the angiogenesis needed for tumor growth and metastasis.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT 476159-98-5, M475271
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel Src kinase inhibitor M475271 inhibits VEGF-induced vascular endothelial-cadherin and β-catenin phosphorylation but increases their association)

L4 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2006:1027913 CAPLUS Full-text
DOCUMENT NUMBER: 146:237
TITLE: N-(5-Chloro-1,3-benzodioxol-4-yl)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5- (tetrahydro-2H-pyran-4-yloxy)quinazolin-4-amine, a Novel, Highly Selective, Orally Available, Dual-Specific c-Src/Abl Kinase Inhibitor
AUTHOR(S): Hennequin, Laurent F.; Allen, Jack; Breed, Jason; Curwen, Jon; Fennell, Michael; Green, Tim P.; Lambert van der Brempt, Christine; Morgentin, Remy; Norman, Richard A.; Olivier, Annie; Otterbein, Ludovic; Ple, Patrick A.; Warin, Nicolas; Costello, Gerard
CORPORATE SOURCE: Centre de Recherches, AstraZeneca, Reims, 51689, Fr.
SOURCE: Journal of Medicinal Chemistry (2006), 49(22), 6465-6488
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 146:237
GI



I

AB Src family kinases (SFKs) are nonreceptor tyrosine kinases that are reported to be critical for cancer progression. We report here a novel subseries of C-5-substituted anilinoquinazolines that display high affinity and specificity for the tyrosine kinase domain of the c-Src and Abl enzymes. These compds. exhibit high selectivity for SFKs over a panel of recombinant protein kinases, excellent pharmacokinetics, and in vivo activity following oral dosing. N-(5-Chloro-1,3-benzodioxol-4-yl)-7-[2-(4- methylpiperazin-1-yl)ethoxy]-5-(tetrahydro-2H-pyran-4-yloxy)quinazolin-4- amine(I) (AZD0530) inhibits c-Src and Abl enzymes at low nanomolar concns. and is highly selective over a range of kinases. AZD0530 displays excellent pharmacokinetic parameters in animal preclinically and in man (t1/2 = 40 h). AZD0530 is a potent inhibitor of

tumor growth in a c-Src-transfected 3T3-fibroblast xenograft model in vivo and led to a significant increase in survival in a highly aggressive, orthotopic model of human pancreatic cancer when dosed orally once daily. AZD0530 is currently undergoing clin. evaluation in man.

REFERENCE COUNT: 108 THERE ARE 108 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT 379231-04-6, AZD0530 401812-23-5 401812-28-0 476159-98-5, M475271 914456-18-1 914456-22-7
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(N-(5-Chloro-1,3-benzodioxol-4-yl)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5- (tetrahydro-2H-pyran-4-yloxy)quinazolin-4-amine, a Novel, Highly Selective, Orally Available, Dual-Specific c-Src/Abl Kinase Inhibitor)

L4 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2006:842429 CAPLUS Full-text

DOCUMENT NUMBER: 145:448747

TITLE: Inhibition of vascular endothelial growth factor (VEGF)-165 and semaphorin 3A-mediated cellular invasion and tumor growth by the VEGF signaling inhibitor ZD4190 in human colon cancer cells and xenografts

AUTHOR(S): Nguyen, Quang-De; Rodrigues, Sylvie; Rodrigue, Christelle M.; Rivat, Christine; Grijelmo, Clara; Bruyneel, Erik; Emami, Shahin; Attoub, Samir; Gespach, Christian

CORPORATE SOURCE: Institut National de la Sante et de la Recherche Medicale, Universite Pierre et Marie Curie-Paris 6, Molecular and Clinical Oncology of Solid Tumors, Hopital Saint-Antoine, Paris, 75571 12, Fr.

SOURCE: Molecular Cancer Therapeutics (2006), 5(8), 2070-2077 CODEN: MCTOCF; ISSN: 1535-7163

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We recently showed by DNA microarray anal. that vascular endothelial growth factor (VEGF) receptor (VEGFR) is expressed in HCT8/S11 human colon cancer cells, suggesting that several angiogenic factors may target colon cancer cells themselves. In this study, transcripts encoding the VEGF-165 and semaphorin 3A (Sema3A) receptors and coreceptors Flt-1, KDR/Flk-1, plexin A1, and neuropilins NP-1 and NP-2 were identified by reverse transcription-PCR in the human colon cancer cell lines HCT8/S11, HT29, HCT116, and PCmsrc. Collagen invasion induced by VEGF-165 and Sema3A in HCT8/S11 cells (EC50, 0.4-1 nmol/L) required p42/44 mitogen-activated protein kinase and signaling through RhoA/Rho-kinase-dependent and -independent pathways, resp. As expected, the VEGFR signaling inhibitor ZD4190 selectively abrogated the proinvasive activity of VEGF in collagen gels (IC50, 10 nmol/L) and chick heart fragments. We identify a novel function for VEGF-165 and Sema3A as proinvasive factors for human colorectal cancer cells. Interestingly, oral administration of the single drug ZD4190 to athymic mice (50 mg/kg/d, once daily) inhibited by 70% the growth of HCT8/S11 tumor cell xenografts. Combinations between the src tyrosine kinase inhibitor M475271 and ZD4190 or cisplatin resulted in additive therapeutic activity against LNM35 human lung tumor xenografts. Our data have significant implications for new therapeutic approaches and individualized treatment targeting VEGFR and src signaling pathways in combination with established clin. drugs at primary tumors and distant metastases in colon and lung cancer patients.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT 15663-27-1, Cisplatin 257938-36-6, ZD4190 476159-98-5, M475271
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of VEGF-165 and semaphorin 3A-mediated cellular invasion and tumor growth by ZD4190 in human colon cancer cells)

L4 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2006:551066 CAPLUS Full-text
DOCUMENT NUMBER: 145:388852
TITLE: Src tyrosine kinase inhibitor, M475271, suppresses subcutaneous growth and production of lung metastasis via inhibition of proliferation, invasion, and vascularization of human lung adenocarcinoma cells
AUTHOR(S): Zheng, Rui; Yano, Seiji; Matsumori, Yuka; Nakataki, Emiko; Muguruma, Hiroaki; Yoshizumi, Masanori; Sone, Saburo
CORPORATE SOURCE: Department of Internal Medicine and Molecular Therapeutics, University of Tokushima Graduate School, Tokushima, Japan
SOURCE: Clinical & Experimental Metastasis (2005), 22(3), 195-204
CODEN: CEXMD2; ISSN: 0262-0898
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Src, a proto-oncogene, has been strongly implicated in the growth, progression and metastasis of a number of human cancers. Its role in lung cancer is, however, still unknown. In the present study, we assessed the expression of Src in three different human lung adenocarcinoma cell lines (PC-9, PC14PE6, A549), and explored the effect of a novel Src kinase inhibitor, M475271, on the behavior of the cell lines. The three cell lines expressed various levels of auto-phosphorylated Src. While M475271 reduced Src-phosphorylation and invasiveness of all three cell lines, it inhibited the proliferation of PC-9 and A549 cells with highly phosphorylated Src, but not PC14PE6 cells. We further examined the effect of M475271 on s.c. tumors and lung metastasis caused by PC-9 and/or A549 cells in NK-cell depleted SCID mice. Daily oral treatment with M475271 inhibited the growth of s.c. tumors with PC-9 and A549 cells via inhibition of tumor cells proliferation, VEGF production and/or vascularization in the mice in a dose-dependent manner. In the metastasis model with A549 cells, the lung weight in the M475271 (50 mg/kg)-treated group was less than that of the control group, despite no difference in the number of metastatic nodules. Our results suggest that inhibition of tyrosine kinase Src by M475271 could reduce the growth, invasion and VEGF-mediated neovascularization of lung adenocarcinoma cells, resulting in inhibition of growth of s.c. tumors and lung metastasis. Therefore, a novel Src tyrosine kinase inhibitor, M475271, might be helpful for controlling the progression of human lung adenocarcinoma.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
IT 476159-98-5, M475271
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(M475271 inhibited s.c. growth and production of lung metastasis through inhibition of proliferation, invasion and vascularization of human lung adenocarcinoma cell in mouse)

L4 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:574839 CAPLUS Full-text
DOCUMENT NUMBER: 144:45221
TITLE: A novel Src kinase inhibitor, M475271, inhibits

VEGF-induced human umbilical vein endothelial cell proliferation and migration

AUTHOR(S): Ali, Nermin; Yoshizumi, Masanori; Fujita, Yoshiko; Izawa, Yuki; Kanematsu, Yasuhisa; Ishizawa, Keisuke; Tsuchiya, Koichiro; Yano, Seiji; Sone, Saburo; Tamaki, Toshiaki

CORPORATE SOURCE: Department of Pharmacology, The University of Tokushima Graduate School Institute of Health Biosciences, Tokushima, 770-8503, Japan

SOURCE: Journal of Pharmacological Sciences (Tokyo, Japan) (2005), 98(2), 130-141
CODEN: JPSTGJ; ISSN: 1347-8613

PUBLISHER: Japanese Pharmacological Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Vascular endothelial growth factor (VEGF) was reported to be a potent proangiogenic factor that plays a pivotal role in both physiol. and pathol. angiogenesis. M475271, 4-quinazolinamine, N-(2-chloro-5- methoxyphenyl)-6-methoxy-7-[(1-methyl-4-piperidinyl)methoxy]-(9Cl), is a new anilinoquinazoline derivative that showed selective inhibition of Src kinase activity and tumor growth in vivo. Here, we examined the effect of M475271 on VEGF-induced human umbilical vein endothelial cell (HUVEC) proliferation and migration and their intracellular mechanisms. Our findings showed that M475271 pretreatment resulted in a significant inhibition of VEGF-induced HUVEC proliferation, [3H]thymidine incorporation, and migration. M475271 inhibited VEGF-induced Flk-1 and Src phosphorylation and their association Confocal laser microscopic examination confirmed the inhibitory effect of M475271 on VEGF-induced Flk-1/Src association M475271 inhibited VEGF-induced extracellular signal-regulated kinase/2 (ERK1/2) and p38 but not Akt activation in a concentration-dependent manner. M475271, PI3-K inhibitor, and p38 inhibitor inhibited VEGF-induced HUVEC proliferation and migration. However, a MEK1/2 inhibitor inhibited VEGF-induced proliferation but not migration. These findings suggest that M475271 attenuates VEGF-induced HUVEC proliferation and migration through the inhibition of signaling pathways involving Src, ERK1/2, and/or p38. Taken together, these data indicate that M475271 may be a useful candidate for inhibition of endothelial cell proliferation and migration relevant to angiogenesis.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT 476159-98-5, M 475271
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(a novel Src kinase inhibitor, M475271, inhibits VEGF-induced human umbilical vein endothelial cell proliferation and migration)

L4 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:995977 CAPLUS Full-text

DOCUMENT NUMBER: 141:420417

TITLE: Therapeutic agents comprising an anti-angiogenic agent in combination with an Src inhibitor for use in normotensive treatment of angiogenesis

INVENTOR(S): Curwen, Jon Owen; Wedge, Stephen Robert

PATENT ASSIGNEE(S): Astrazeneca AB, Swed.; Astrazeneca UK Limited

SOURCE: PCT Int. Appl., 111 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004098604	A1	20041118	WO 2004-GB1939	20040504
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004237132	A1	20041118	AU 2004-237132	20040504
AU 2004237132	B2	20071018		
CA 2519930	A1	20041118	CA 2004-2519930	20040504
EP 1620104	A1	20060201	EP 2004-731049	20040504
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, HR				
BR 2004009742	A	20060509	BR 2004-9742	20040504
CN 1784232	A	20060607	CN 2004-80012089	20040504
JP 2006525304	T	20061109	JP 2006-506222	20040504
NO 2005004411	A	20051130	NO 2005-4411	20050923
US 20060223815	A1	20061005	US 2005-555389	20051103
MX 2005PA11858	A	20060217	MX 2005-PA11858	20051104
PRIORITY APPLN. INFO.:			GB 2003-10401 A	20030507
			WO 2004-GB1939 W	20040504

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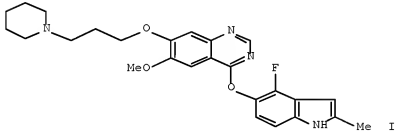
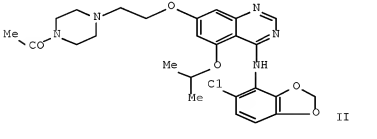


I



II

AB The invention relates to the use of an anti-angiogenic agent, such as I (preparation given), in combination with an inhibitor of the Src family of non-receptor tyrosine kinases, such as the II (prepns. according to a previous patent given), in the manufacture of a medicament for use in the substantially normotensive treatment in a warm-blooded mammal such as a human being of a

disease state associated with angiogenesis. The invention provides for the Src kinase inhibitor to be administered in an amount effective to counteract substantially the hypertension induced by the anti-angiogenic agent. Thus, 7-(2-chloroethoxy)-4-(6-chloro-2,3- methylenedioxyanilino)-5-isopropoxyquinazoline was coupled with 1-acetylpiperazine using KI in DMA to give I. The diastolic blood pressure profile of rats over a 24 h period after administration of a combination of 1.5 mg/kg of I and 25 mg/kg of II demonstrated that the contrasting blood pressure effects of the antiangiogenic agent and the Src kinase inhibitor were substantially counterbalanced.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT 379230-84-9, 4-(2,4-Dichloro-5-methoxyanilino)-7-[2-(piperidino)ethoxy]-5-[(tetrahydropyran-4-yl)oxy]quinazoline 379230-85-0, 4-(2,4-Dichloro-5-methoxyanilino)-7-[2-(morpholino)ethoxy]-5-[(tetrahydropyran-4-yl)oxy]quinazoline 379231-01-3, 4-(6-Chloro-2,3-methylenedioxyanilino)-7-[2-(pyrrolidin-1-yl)ethoxy]-5-[(tetrahydropyran-4-yl)oxy]quinazoline 379231-02-4, 4-(6-Chloro-2,3-methylenedioxyanilino)-7-[3-(pyrrolidin-1-yl)propoxy]-5-[(tetrahydropyran-4-yl)oxy]quinazoline 379231-04-6, 4-(6-Chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-[(tetrahydropyran-4-yl)oxy]quinazoline 379231-05-7, 4-(6-Chloro-2,3-methylenedioxyanilino)-7-[2-(piperidino)ethoxy]-5-[(tetrahydropyran-4-yl)oxy]quinazoline 401811-21-0, 4-(6-Chloro-2,3-methylenedioxyanilino)-7-[3-(4-isobutyrylpiperazin-1-yl)propoxy]-6-methoxyquinazoline 401812-18-8, 6-Methoxy-4-(2,3-methylenedioxyanilino)-7-[3-(morpholino)propoxy]quinazoline 401812-20-2, 6-Methoxy-4-(2,3-methylenedioxyanilino)-7-[3-(pyrrolidin-1-yl)propoxy]quinazoline 401812-21-3, 6-Methoxy-4-(2,3-methylenedioxyanilino)-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline 401812-22-4, 6-Methoxy-4-(2,3-methylenedioxyanilino)-7-[3-(piperidino)propoxy]quinazoline 476159-98-5, 4-(2-Chloro-5-methoxyanilino)-6-methoxy-7-[(N-methylpiperidin-4-yl)methoxy]quinazoline 476160-42-6, 4-(2-Chloro-5-methoxyanilino)-6-methoxy-7-[(piperidin-4-yl)methoxy]quinazoline 476162-74-0, 4-(2,4-Dichloro-5-methoxyanilino)-6-methoxy-7-[(N-methylpiperidin-4-yl)methoxy]quinazoline 476162-76-2, 4-(2,4-Dichloro-5-methoxyanilino)-6-methoxy-7-[(piperidin-4-yl)methoxy]quinazoline 692054-06-1, 7-[2-(4-Acetylpiperazin-1-yl)ethoxy]-4-[(5-chloro-2,3-methylenedioxypyridin-4-yl)amino]-5-isopropoxyquinazoline 692054-28-7, 7-[2-(4-Acetylpiperazin-1-yl)ethoxy]-4-[(5-chloro-2,3-methylenedioxypyridin-4-yl)amino]-5-[(tetrahydropyran-4-yl)oxy]quinazoline 692054-33-4 692054-44-7

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Src kinase inhibitor; therapeutic agents comprising an anti-angiogenic agent in combination with an Src inhibitor for use in normotensive treatment of angiogenesis)

L4 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:857372 CAPLUS Full-text
DOCUMENT NUMBER: 141:350196
TITLE: Preparation of quinazoline derivatives as selective Src kinase inhibitors
INVENTOR(S): Curwen, Jon Owen
PATENT ASSIGNEE(S): Astrazeneca Ab, Swed.; Astrazeneca UK Limited
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2004087120	A2	20041014	WO 2004-GB1286	20040323
WO 2004087120	A3	20050127		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2003-7333 A 20030329

AB The invention relates to the use of quinazoline derivative as a Src kinase inhibitor in the production of a medicament for use in the prophylaxis or treatment of hypertension. More particularly, the invention concerns the anti-hypertensive use of a selective Src kinase inhibitor that possess less potent VEGF receptor tyrosine kinase inhibitory properties. The invention also relates to a combination product comprising a Src kinase inhibitor and one or more further anti-hypertensive agents and to the use of Src kinase inhibitors as primary regulators of cardiovascular disease and in the prevention of stroke. For example, 7-[2-(4-acetylpiperazin-1- yl)ethoxy]-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5- isopropoxyquinazoline administered to rats at 25 mg/kg p.o. on day 1 showed hypotensive effect of 25 mmHg on day 2.

IT 379230-84-9P, 4-(2,4-Dichloro-5-methoxyanilino)-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline 379230-85-0P, 4-(2,4-Dichloro-5-methoxyanilino)-7-(2-morpholinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline 379230-86-1P, 4-(2,4-Dichloro-5-methoxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline 379230-87-2P, 4-(2-Bromo-5-methoxyanilino)-7-(2-pyrrolidin-1-ylethoxy)-5-tetrahydropyran-4-yloxyquinazoline 379231-01-3P, 4-(6-Chloro-2,3-methylenedioxyanilino)-7-(2-pyrrolidin-1-ylethoxy)-5-tetrahydropyran-4-yloxyquinazoline 379231-03-5P, 4-(6-Chloro-2,3-methylenedioxyanilino)-7-[3-(4-methylpiperazin-1-yl)propoxy]-5-tetrahydropyran-4-yloxyquinazoline 379231-05-7P, 4-(6-Chloro-2,3-methylenedioxyanilino)-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline 401810-94-4P, 6-Methoxy-4-(2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]quinazoline 401812-18-8P, 6-Methoxy-4-(2,3-methylenedioxyanilino)-7-(3-morpholinopropoxy)quinazoline 401812-19-9P, 6-Methoxy-4-(2,3-methylenedioxyanilino)-7-[3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy]quinazoline 401812-20-2P, 6-Methoxy-4-(2,3-methylenedioxyanilino)-7-[3-(pyrrolidin-1-yl)propoxy]quinazoline 401812-21-3P, 6-Methoxy-4-(2,3-methylenedioxyanilino)-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline 476159-98-5P, 4-(2-Chloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline 476160-42-6P, 4-(2-Chloro-5-methoxyanilino)-6-methoxy-7-piperidin-4-ylmethoxyquinazoline 476160-43-7P, 4-(2-Bromo-5-methoxyanilino)-6-methoxy-7-[2-(N-methylpiperidin-4-yl)ethoxy]quinazoline 476162-74-0P, 4-(2,4-Dichloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline 476162-76-2P, 4-(2,4-Dichloro-5-methoxyanilino)-6-methoxy-7-piperidin-4-ylmethoxyquinazoline 476162-77-3P, 4-(2,4-Dichloro-5-methoxyanilino)-6-methoxy-7-[2-(N-methylpiperidin-4-yl)ethoxy]quinazoline 692053-13-7P, 4-(5-Chloro-2,3-methylenedioxypyridin-4-ylamino)-6-methoxy-7-[3-(4-prop-2-ynylpiperazin-1-yl)propoxy]quinazoline 692054-06-1P, 7-[2-(4-Acetylpiperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxypyridin-4-ylamino)-5-isopropoxyquinazoline 692054-11-8P,

4-(5-Chloro-2,3-methylenedioxypyridin-4-ylamino)-6-methoxy-7-[3-(4-isobutyrylpiperazin-1-yl)propoxy]quinazoline 692054-16-3P, 4-(5-Chloro-2,3-methylenedioxypyridin-4-ylamino)-6-Methoxy-7-[3-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]propoxy]quinazoline 692054-22-1P, 4-(5-Chloro-2,3-methylenedioxypyridin-4-ylamino)-6-methoxy-7-[2-(4-prop-2-ynylpiperazin-1-yl)ethoxy]quinazoline 692054-28-7P, 4-(5-Chloro-2,3-methylenedioxypyridin-4-ylamino)-7-[2-(4-acetylpiperazin-1-yl)ethoxy]-5-(tetrahydropyran-4-yloxy)quinazoline 692054-33-4P, 4-(5-Chloro-2,3-methylenedioxypyridin-4-ylamino)-5-(tetrahydropyran-4-yloxy)-7-[2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]ethoxy]quinazoline
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of quinazoline derivs. as selective Src kinase inhibitors and regulators of cardiovascular disease for prophylaxis or treatment of hypertension or for prevention of stroke)

L4 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:430753 CAPLUS Full-text
DOCUMENT NUMBER: 141:1220
TITLE: Preparation of quinazolines as Src family non-receptor tyrosine kinase inhibitors for use in combination therapy with gemcitabine for treatment and prophylaxis of pancreatic cancer
INVENTOR(S): Barge, Alan
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.; Astrazeneca UK Limited
SOURCE: PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004043472	A1	20040527	WO 2003-GB4787	20031107
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2504666	A1	20040527	CA 2003-2504666	20031107
AU 2003279456	A1	20040603	AU 2003-279456	20031107
AU 2003279456	B2	20070517		
EP 1562612	A1	20050817	EP 2003-772404	20031107
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003016170	A	20050927	BR 2003-16170	20031107
CN 1711094	A	20051221	CN 2003-80103138	20031107
JP 2006508953	T	20060316	JP 2004-550784	20031107
NZ 539514	A	20071130	NZ 2003-539514	20031107
NO 2005002312	A	20050606	NO 2005-2312	20050511
ZA 2005003805	A	20060927	ZA 2005-3805	20050511
MX 2005PA05119	A	20050802	MX 2005-PA5119	20050512
US 20060142297	A1	20060629	US 2005-534721	20051020

PRIORITY APPLN. INFO.: GB 2002-26434 A 20021113
WO 2003-GB4787 W 20031107

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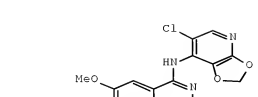


I

AB The invention concerns a combination comprising an inhibitor of Src kinase and the cytotoxic agent, gemcitabine, a pharmaceutical composition comprising such a combination, and its use in the treatment or prophylaxis of cancer, particularly of pancreatic cancer. Examples include prepns. for anilino- and (pyridylamino)quinazoline Src inhibitors (no Markush structure given) and bioassays demonstrating the synergistic effect of treating pancreatic cancer with a quinazoline Src inhibitor in combination with gemcitabine. For instance, 4-amino-5-chloro-2,3-methylenedioxypyridine was coupled with 4-chloro-7-(3-chloropropoxy)-6-methoxyquinazoline (preparation of reactants given) in the presence of sodium hexamethyldisilazane in THF to afford the (pyridylamino)quinazoline I. Nude mice were injected with pancreatic tumor cells derived from the COLO 357 human pancreatic cancer cell line and treated with gemcitabine, the Src inhibitor, 4-(2-chloro-5- methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline, or a combination of the two. Evaluation for tumor growth and incidence of liver metastases showed that, compared with the weight of control tumors, tumor growth in animals treated with the combination was much reduced (1359 mg and 124 mg, resp.) to a level well below that achievable on the dosing of either gemcitabine or the Src inhibitor alone. In addition, there was no liver metastasis in the animals treated with the combination, whereas liver metastasis was present in 1/5 of the animals treated with gemcitabine alone.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT 379231-01-3P, 4-(6-Chloro-2,3-methylenedioxyanilino)-7-[2-(pyrrolidin-1-yl)ethoxy]-5-[(tetrahydropyran-4-yl)oxy]quinazoline 379231-04-6P, 4-(6-Chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-[(tetrahydropyran-4-yl)oxy]quinazoline 379231-05-7P, 4-(6-Chloro-2,3-methylenedioxyanilino)-7-[2-(piperidino)ethoxy]-5-[(tetrahydropyran-4-yl)oxy]quinazoline 401812-18-8P, 6-Methoxy-4-(2,3-methylenedioxyanilino)-7-[3-(morpholino)propoxy]quinazoline 476159-98-5P, 4-(2-Chloro-5-methoxyanilino)-6-methoxy-7-[(N-methylpiperidin-4-yl)methoxy]quinazoline 692053-13-7P, 4-[(5-Chloro-2,3-methylenedioxypyridin-4-yl)amino]-6-methoxy-7-[3-[4-(prop-2-ynyl)piperazin-1-yl]propoxy]quinazoline 692053-49-9P, 4-[(5-Chloro-2,3-methylenedioxypyridin-4-yl)amino]-7-hydroxy-5-isopropoxyquinazoline 692053-63-7P, 7-(2-Chloroethoxy)-4-[(2,3-methylenedioxypyridin-4-yl)amino]-6-methoxyquinazoline 692053-68-2P, 7-(3-Chloropropoxy)-4-[(2,3-methylenedioxypyridin-4-yl)amino]-6-methoxyquinazoline 692053-72-8P, 7-[2-(4-Acetylpiperazin-1-yl)ethoxy]-4-[(2,3-methylenedioxypyridin-4-yl)amino]-5-[(tetrahydropyran-4-yl)oxy]quinazoline 692053-76-2P, 7-[2-(4-Acetylpiperazin-1-yl)ethoxy]-4-[(2,3-methylenedioxypyridin-4-yl)amino]-5-isopropoxyquinazoline 692053-82-0P, 4-[(5-Chloro-2,3-methylenedioxypyridin-4-yl)amino]-7-[2-[4-

(2-dimethylaminoacetyl)piperazin-1-yl]ethoxy]-5-isopropoxyquinazoline 692054-00-5P, 4-[(5-Chloro-2,3-methylenedioxypyridin-4-yl)amino]-7-[[1-(2-dimethylaminoacetyl)piperidin-4-yl]methoxy]-6-methoxyquinazoline 692054-06-1P, 5-Isopropoxy-7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-[(5-chloro-2,3-methylenedioxypyridin-4-yl)amino]quinazoline 692054-11-8P, 6-Methoxy-7-[3-(4-isobutyrylpiperazin-1-yl)propoxy]-4-[(5-chloro-2,3-methylenedioxypyridin-4-yl)amino]quinazoline 692054-16-3P, 6-Methoxy-7-[3-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]propoxy]-4-[(5-chloro-2,3-methylenedioxypyridin-4-yl)amino]quinazoline 692054-22-1P, 6-Methoxy-7-[2-[4-(prop-2-ynyl)piperazin-1-yl]ethoxy]-4-[(5-chloro-2,3-methylenedioxypyridin-4-yl)amino]quinazoline 692054-28-7P, 5-[(Tetrahydropyran-4-yl)oxy]-7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-[(5-chloro-2,3-methylenedioxypyridin-4-yl)amino]quinazoline 692054-33-4P 692054-44-7P 692054-49-2P, 6-[2-(Morpholino)ethoxy]-7-methoxy-4-[(5-chloro-2,3-methylenedioxypyridin-4-yl)amino]quinazoline 692054-55-0P, 6-[2-(4-Methylpiperazin-1-yl)ethoxy]-7-methoxy-4-[(5-chloro-2,3-methylenedioxypyridin-4-yl)amino]quinazoline 692054-60-7P, 6-[2-(Pyrrolidin-1-yl)ethoxy]-7-methoxy-4-[(5-chloro-2,3-methylenedioxypyridin-4-yl)amino]quinazoline 692054-66-3P, 6-[2-(4-Acetylpiperazin-1-yl)ethoxy]-7-methoxy-4-[(5-chloro-2,3-methylenedioxypyridin-4-yl)amino]quinazoline 692054-72-1P 692054-77-6P, 6-[3-(Pyrrolidin-1-yl)propoxy]-7-methoxy-4-[(5-chloro-2,3-methylenedioxypyridin-4-yl)amino]quinazoline 692054-83-4P, 6-[3-(Morpholino)propoxy]-7-methoxy-4-[(5-chloro-2,3-methylenedioxypyridin-4-yl)amino]quinazoline 692054-88-9P, 6-[3-(4-Acetylpiperazin-1-yl)propoxy]-7-methoxy-4-[(5-chloro-2,3-methylenedioxypyridin-4-yl)amino]quinazoline 692054-94-7P, 6-[3-(4-Methylpiperazin-1-yl)propoxy]-7-methoxy-4-[(5-chloro-2,3-methylenedioxypyridin-4-yl)amino]quinazoline 692055-00-8P 692055-04-2P, 5-[(Tetrahydropyran-4-yl)oxy]-7-[2-[4-(prop-2-ynyl)piperazin-1-yl]ethoxy]-4-[(5-chloro-2,3-methylenedioxypyridin-4-yl)amino]quinazoline 692055-10-0P, 5-[(Tetrahydropyran-4-yl)oxy]-7-[2-(morpholino)ethoxy]-4-[(5-chloro-2,3-methylenedioxypyridin-4-yl)amino]quinazoline 692055-16-6P, 5-[(Tetrahydropyran-4-yl)oxy]-7-[3-(morpholino)propoxy]-4-[(5-chloro-2,3-methylenedioxypyridin-4-yl)amino]quinazoline 692055-22-4P, 5-[(Tetrahydropyran-4-yl)oxy]-7-[3-[4-(prop-2-ynyl)piperazin-1-yl]propoxy]-4-[(5-chloro-2,3-methylenedioxypyridin-4-yl)amino]quinazoline 692055-34-8P, 5-Isopropoxy-7-[2-[4-(2-hydroxyethyl)piperazin-1-yl]ethoxy]-4-[(5-chloro-2,3-methylenedioxypyridin-4-yl)amino]quinazoline 692055-41-7P, 5-Isopropoxy-7-[2-(pyrrolidin-1-yl)ethoxy]-4-[(5-chloro-2,3-methylenedioxypyridin-4-yl)amino]quinazoline 692055-46-2P, 5-Isopropoxy-7-[2-(piperidino)ethoxy]-4-[(5-chloro-2,3-methylenedioxypyridin-4-yl)amino]quinazoline 692055-53-1P, 5-Isopropoxy-7-[2-(morpholino)ethoxy]-4-[(5-chloro-2,3-methylenedioxypyridin-4-yl)amino]quinazoline 692055-59-7P, 5-Isopropoxy-7-[2-[4-(prop-2-ynyl)piperazin-1-yl]ethoxy]-4-[(5-chloro-2,3-methylenedioxypyridin-4-yl)amino]quinazoline 692055-66-6P 692055-76-8P, 5-Isopropoxy-7-[2-(4-methylpiperazin-1-yl)ethoxy]-4-[(5-chloro-2,3-methylenedioxypyridin-4-yl)amino]quinazoline 692055-83-7P, 5-Isopropoxy-7-[3-(morpholino)propoxy]-4-[(5-chloro-2,3-methylenedioxypyridin-4-yl)amino]quinazoline 692055-88-2P, 7-[3-(Morpholino)propoxy]-4-[(5-chloro-2,3-methylenedioxypyridin-4-yl)amino]quinazoline 692055-94-0P, 7-[3-(4-Acetylpiperazin-1-yl)propoxy]-4-[(5-chloro-2,3-methylenedioxypyridin-4-yl)amino]quinazoline 692056-00-1P, 6-Methoxy-7-[2-[4-(prop-2-ynyl)piperazin-1-yl]ethoxy]-4-[(2,3-methylenedioxypyridin-4-yl)amino]quinazoline 692056-04-5P, 6-Methoxy-7-[3-[4-(prop-2-ynyl)piperazin-1-yl]propoxy]-4-[(2,3-methylenedioxypyridin-4-yl)amino]quinazoline 694439-00-4P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES

(Uses)
(antitumor agent; preparation of quinazoline-containing Src inhibitors for use
in synergistic combination with gemcitabine for treatment and prophylaxis of pancreatic cancer)

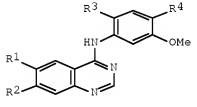
L4 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:45404 CAPLUS Full-text
DOCUMENT NUMBER: 140:228458
TITLE: Discovery of a New Class of Anilinoquinazoline Inhibitors with High Affinity and Specificity for the Tyrosine Kinase Domain of c-Src
AUTHOR(S): Ple, Patrick A.; Green, Tim P.; Hennequin, Laurent F.; Curwen, Jon; Fennell, Michael; Allen, Jack; Lambert-van der Brempt, Christine; Costello, Gerard
CORPORATE SOURCE: Centre de Recherches, AstraZeneca, Reims, 51689, Fr.
SOURCE: Journal of Medicinal Chemistry (2004), 47(4), 871-887 CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 140:228458
AB Deregulated activity of the nonreceptor tyrosine kinase c-Src is believed to result in signal transduction, cytoskeletal and adhesion changes, ultimately promoting a tumor-invasive phenotype. We report here the discovery of a new class of anilinoquinazoline inhibitors with high affinity and specificity for the tyrosine kinase domain of the c-Src enzyme. Special attention was directed toward finding inhibitors selective against KDR tyrosine kinase in order to ensure that the in vivo profile of a specific Src inhibitor could be determined The 4-aminobenzodioxole quinazoline series gave compds. with excellent potency and selectivity. The most interesting compds. were evaluated in vivo and displayed good pharmacokinetics following oral dosing. Compds. such as the aminobenzodioxoles were shown to be potent inhibitors of tumor growth in a c-Src-transformed 3T3 xenograft model in vivo, resulting in more than 90% growth inhibition at doses as low as 6 mg/kg po once daily. Src tyrosine kinase inhibitors such as these may provide a novel therapeutic modality for targeting cancer invasion and metastasis.
REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
IT 288383-44-8P 401810-57-9P 401810-71-7P 401811-07-2P 412335-85-4P 412336-95-9P 412349-32-7P 412349-36-1P 412349-40-7P 418811-70-8P 418811-76-4P 476159-98-5P 667875-97-0P 667875-98-1P 667875-99-2P 667876-00-8P 667876-01-9P 667876-02-0P 667876-03-1P 667876-04-2P 667876-05-3P 667876-06-4P 667876-07-5P 667876-08-6P 667876-09-7P 667876-10-0P
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and structure-activity relationship of new class of anilinoquinazoline inhibitors with high affinity and specificity for tyrosine kinase domain of c-Src)

L4 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:888721 CAPLUS Full-text
DOCUMENT NUMBER: 137:384856
TITLE: Preparation of 4-anilinoquinazolines as antitumor agents
INVENTOR(S): Hennequin, Laurent Francois Andre; Ple, Patrick
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.; Astrazeneca UK Limited
SOURCE: PCT Int. Appl., 78 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002092578	A1	20021121	WO 2002-GB2124	20020508
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002302736	A1	20021125	AU 2002-302736	20020508
PRIORITY APPLN. INFO.:			EP 2001-401222 A	20010514
			WO 2002-GB2124 W	20020508

OTHER SOURCE(S): MARPAT 137:384856
GI



I

AB The title compds. [I; R1 = H, alkoxy and R2 = X1Q1 (wherein X1 = O, S, SO, etc.; Q1 = heteroaryl, heteroarylalkyl, heterocyclyl, etc.), X2R5 (wherein X2 = O, NH, Nalkyl; R5 = hydroxyalkyl, alkoxyalkyl, aminoalkyl, etc.); or R2 = H, alkoxy and R1 = X1Q1, X2R5; R3, R4 = Cl, Br, I], useful as anti-invasive agents in the containment and/or treatment of solid tumor disease, were prepared and formulated. E.g., a multi-step synthesis of I.2HCl [R1 = OMe; R2 = N-methylpiperidin-4-ylmethoxy; R3, R4 = Cl], starting from Et piperidine-4-carboxylate, was given. Biol. activity of compds. I was tested in 4 tests. Thus, the compds. I showed IC50 of 0.001-10 μM in in vitro c-Src tyrosine kinase assay.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

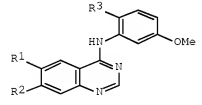
IT 476162-53-5P, 4-(2,4-Dichloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline dihydrochloride salt
476162-54-6P 476162-56-8P 476162-58-0P 476162-59-1P 476162-60-4P
476162-62-6P 476162-66-0P 476162-68-2P 476162-70-6P,
4-(2,4-Dichloro-5-methoxyanilino)-6-methoxy-7-(2-hydroxy-3-piperidinopropoxy)quinazoline dihydrochloride salt 476162-72-8P,
4-(2,4-Dichloro-5-methoxyanilino)-7-[2-hydroxy-3-(N-isopropyl-N-methylamino)propoxy]-6-methoxyquinazoline dihydrochloride salt
476162-74-0P, 4-(2,4-Dichloro-5-methoxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline 476162-76-2P,
4-(2,4-Dichloro-5-methoxyanilino)-6-methoxy-7-piperidin-4-

ylmethoxyquinazoline 476162-77-3P, 4-(2,4-Dichloro-5-methoxyanilino)-6-methoxy-7-[2-(N-methylpiperidin-4-yl)ethoxy]quinazoline 476162-78-4P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 4-anilinoquinazolines as antitumor agents)

L4 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:888720 CAPLUS Full-text
DOCUMENT NUMBER: 137:384855
TITLE: Preparation of 4-anilinoquinazolines as antitumor agents
INVENTOR(S): Hennequin, Laurent Francois Andre; Ple, Patrick
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.; Astrazeneca UK Limited
SOURCE: PCT Int. Appl., 96 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002092577	A1	20021121	WO 2002-GB2117	20020508
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002256776	A1	20021125	AU 2002-256776	20020508
PRIORITY APPLN. INFO.:			EP 2001-401223 A	20010514
			WO 2002-GB2117 W	20020508

OTHER SOURCE(S): MARPAT 137:384855
GI



I

AB The title compds. [I; R1 = H, alkoxy and R2 = X1Q1 (wherein X1 = O, S, SO, etc.; Q1 = heteroaryl, heteroarylalkyl, heterocyclyl, etc.), X2R5 (wherein X2 = O, NH, Nalkyl; R5 = hydroxyalkyl, alkoxyalkyl, aminoalkyl, etc.); or R2 = H, alkoxy and R1 = X1Q1, X2R5; R3 = Cl, Br, I], useful as anti-invasive agents in the containment and/or treatment of solid tumor disease, were prepared and formulated. E.g., a multi-step synthesis of I [R1 = OMe; R2 = N-methylpiperidin-4-ylmethoxy; R3 = Cl], starting from Et piperidine-4-carboxylate, was given. Biol. activity of compds. I was tested in 4 tests.

Thus, the compds. I showed IC50 of 0.001-10 μM in in vitro c-Src tyrosine kinase assay.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT 476159-98-5P, 4-(2-Chloro-5-methoxyanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline 476159-99-6P, 4-(2-Chloro-5-methoxyanilino)-6-methoxy-7-piperidin-4-ylmethoxyquinazoline monohydrochloride salt 476160-00-6P, 4-(2-Bromo-5-methoxyanilino)-6-methoxy-7-[2-(N-methylpiperidin-4-yl)ethoxy]quinazoline dihydrochloride salt 476160-01-7P 476160-02-8P 476160-03-9P 476160-04-0P 476160-05-1P 476160-06-2P 476160-07-3P 476160-08-4P, 4-(2-Chloro-5-methoxyanilino)-6-methoxy-7-[2-(4-pyridyloxy)ethoxy]quinazoline 476160-09-5P 476160-10-8P 476160-11-9P 476160-12-0P 476160-13-1P 476160-14-2P 476160-15-3P 476160-17-5P 476160-18-6P 476160-19-7P 476160-20-0P 476160-21-1P 476160-22-2P 476160-23-3P 476160-24-4P 476160-25-5P 476160-26-6P 476160-27-7P 476160-28-8P 476160-29-9P 476160-30-2P 476160-31-3P 476160-32-4P 476160-33-5P 476160-34-6P 476160-35-7P 476160-36-8P 476160-37-9P 476160-38-0P 476160-39-1P 476160-40-4P 476160-41-5P 476160-42-6P, 4-(2-Chloro-5-methoxyanilino)-6-methoxy-7-piperidin-4-ylmethoxyquinazoline 476160-43-7P, 4-(2-Bromo-5-methoxyanilino)-6-methoxy-7-[2-(N-methylpiperidin-4-yl)ethoxy]quinazoline
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 4-anilinoquinazolines as antitumor agents)

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